REMARKS

The Applicants respectfully request that the Examiner enter and consider the amendments to the claims as set forth herein.

Claims 1-10 and 20 are pending in the application. Claims 11-19 and 21 were previously withdrawn. Claims 1, 2, 5 and 7 are amended in this response. Claims 3, 4, 6, 8-19 and 21 are canceled, without prejudice, in this response. The amendments to claims 1, 2, 5 and 7 are submitted in the present response solely in an effort to further prosecution. By these amendments Applicants do not disclaim any subject matter to which they are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997). Full support for the amendments is found in the specification. No new matter has been added by these amendments.

I. Claim rejections under 35 U.S.C. § 112, first paragraph 1, for failure to comply with the written description requirement

The Examiner has rejected Claims 1-10 and 20 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Office Action of 8 August 2007 at pages 4-5.

The Examiner states:

> While claimed method is drawn to in vivo treating a patient by administering any cupredoxin comprising the mutant and truncated azurin and other species of cupredoxin. However, the specification only provides the teaching on treating a subject with wild type azurin, not other cupredoxin including elected species of plastocyanin and mutants or truncated azurin of SEQ ID NO: 6 and 7. As such, one skilled in the art would not convince that the applicant had the possession of the claimed method of using any form of cupredoxin except of wild type of azurin.

Id. at page 4 (emphasis in original). Claims 3, 4, 6 and 8-10 are canceled in this response. Applicants respectfully traverse the rejection of claims 1, 2, 5, 7 and 20.

Without acquiescing to the propriety of the Examiner's rejections and solely in an effort to further prosecution, claims 1, 2 and 5 have been amended to recite an azurin, a mutant azurin or a truncated azurin. Support for these amendments is found in the specification as filed. *See, e.g.,* paragraphs [014], [019-025] and [027-031] corresponding to Figures 4-10 and 12-15, respectively, [026], [071], [078], [081], [083-086] and [0112-0120]. Without acquiescing to the propriety of the Examiner's rejections and solely in an effort to

further prosecution, claim 7 has been amended to recite, "wherein the mutant azurin comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 6, 7, 45, 46, 47, 48, 50, 51, 52 and 53." Support for this amendment is found in the specification as filed. *See, e.g.,* paragraphs [083] and [0165].

A. The Examiner's rejection applies improper standards

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003). An applicant complies with the written description requirement by describing the invention using "such descriptive means as words, structures, figures, diagrams, formulas, etc. that set forth the claimed invention." *Regents of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1666 (Fed. Cir. 1997). The written description requirement does not demand that the applicant have literal support in the specification for the claim language. *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983).

The Examiner's rejection misapplies or ignores these well-established standards. For example, the Examiner states that "description of in vitro assay of cytotoxicity to the cancer cells do not render applicant having a possession of in vivo treating a patient with cancer." Office Action of 8 August 2007 at page 6. However, this statement does not apply an appropriate written description standard. The specification does not need to teach in vivo administering for every compound claimed. All that is required is to establish that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Kaslow,* 707 F.2d at 1375. Moreover, it is an established principle that in vivo testing data is not required to show a compound has therapeutic utility: "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process." MPEP § 2107.03. *See also id.* ("Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders, even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims."

(citations omitted)).[1]

Moreover, an applicant is not required to provide any working example in the specification. "A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language." *Falko-Gunter Falkner v. Inglis,* 448 F.3d 1357, 1366 (Fed. Cir. 2006) (quoting *Lizardtech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005)). Only enough must be included to convince a person of skill in the art that the inventor possessed the invention. *Id.* Hence, lack of providing exact examples is not required.

B. Applicants' disclosure is sufficient to convey that they have possession of the claimed invention

To the extent the Examiner's rejection is based upon an assertion that the compounds identified in the method claims are inadequately described, Applicants respectfully disagree. As a preliminary matter, the compound recited in claim 7 as amended is specifically identified by sequence; Applicants cannot contemplate a clearer description of a compound. Independent claim 1 is amended to recite an azurin, a mutant azurin or a truncated azurin. Support for an azurin or a truncated or mutant azurin is provided throughout the present application. As the Examiner admits, "the paragraphs 112-120 of specification teach a method of making mutants and fragments of azurin." Office Action of 8 August 2007 at page 4. *See also* Examples 19-21 and Figures 11-13. *See also* U.S. Patent Ser. No. 7,089,105 (Application Ser. No. 10/047,710, filed 15 January 2002, from which the present application claims priority) which is coextensive with the present application and specifically discloses and claims truncated cupredoxins. As taught in paragraph [0112], mutations and/or truncations of cytotoxic factors can produce cytotoxic agents of varying compositions also demonstrating functional activity. Paragraphs [0112-0120] teach how to develop a truncated or mutant cupredoxin from azurin. Moreover, Examples 19-21 and Figures 11-13 teach that such azurins do induce apoptosis and/or cell cytotoxicity.

[1] Applicants' search of the Patent Office's issued patent database for patents containing "in vitro" and not "in vivo" yielded nearly 33,000 hits. Applicants' search of the Patent Office's issued patent database for patents containing "in vitro" but not "in vivo" in the specification and having "method of treating a patient" in the claims yielded 255 hits.

The Examiner argues that the skilled artisan cannot envision the detailed chemical structure(s) and functional attributes(s) of the encompassed genus of compounds used in the method. Office Action of 8 August 2007 at page 5. However, the written description requirement for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. *See Amgen v. Hoechst Marion Roussel*, 314 F.3d 1313, 1332 (Fed. Cir. 2003); *Eli Lilly,* 119 F.3d at 1568.

In the present application, the genus of compounds recited in claim 1 as amended encompasses an azurin, a mutant azurin or a truncated azurin. The specification teaches identifying characteristics, chemical similarities such as being electron transfer proteins and structural similarities of numerous azurin derivatives. *See, e.g.*, paragraphs [071] and [0112-0120], and Figure 11 for a comparison of azurin mutations. More importantly, the specification also identifies a key conserved structural characteristic. The specification shows azurin to be capable of binding to p53 protein via a hydrophobic patch. *See* paragraphs [081-088]. The specification further describes the cell-death promoting activity of azurin and azurin mutants. Azurin's cytotoxicity is "dependent upon the tumor cell having a functional p53 tumor suppressor gene" (paragraph [087]), and is effected by mutants possessing an intact hydrophobic region and capable of binding p53 (paragraph [084]). Azurin's arrest of cell growth is independent of p53 binding, as evidenced by the cell death activity of mutant azurin M44KM64E, which lacks p53 binding activity (paragraph [086]). *See also* "Programmed Cell Death," 1995 Annual Report, Howard Hughes Medical Institute (Exhibit 1 of Applicants' Response filed 9 October 2007). In addition, it is reported that azurin has a G-H loop sequence which has high binding affinity for ephrinB2, and which exhibits a cytotoxic effect. *See* A. Chaudhari *et al.*, BIOCHEM. 46(7):1799-1810 (2007) (Exhibit 2 of Applicants' Response filed 9 October 2007). It is known in the art that one 18-amino acid truncation of azurin in particular, Azu-113, has significant structural similarity to ephrinB2 at the G-H loop region and selectively binds the ephrinB2 receptor tyrosine kinase EphB2. Exhibit 2. The ability of this azurin truncation to induce cell death "can thus be ascribed to interference in EphB2 signaling." *Id.* Thus, based on the written description and knowledge in the art as to the p53 and EphB2 binding of azurin and mutants and truncations thereof, one skilled in the

art can reasonably conclude that the inventor had possession of the claimed invention.

In addition, the specification teaches how to develop mutants (Example 19), how to use these mutants for in vitro assays (Examples 20 and 21), and that a mutant can be used for treatment of cancer (paragraph [010]. Furthermore, the specification teaches in Examples 15, 16 and 18 how to administer azurins to a patient in vivo. Because the specification teaches how to make the claimed azurins and how to administer the azurins of the present invention to a patient for treatment, one skilled in the art must reasonably conclude that the inventor had possession of the claimed invention.

For all the foregoing reasons, Applicants respectfully request that the Examiner remove the rejection of Claims 1, 2, 5, 7 and 20 for failure to comply with the written description requirement.

II. Claim rejections under 35 U.S.C. § 112, first paragraph, for failure to comply with the enablement requirement

The Examiner rejected Claims 1-11 and 20 under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. Office Action of 8 August 2007 at pages 5-10. Specifically, the Examiner stated the pending claims are rejected because:

> the specification, while being enabling for a method of treating a condition related to resistance to cell death comprising administering to a patient a pharmaceutical composition of wild type azurin of SEQ ID NO:1 does not reasonably provide enablement for the method of administering any other cupredoxin comprising elected plastocyanin and mutated or truncated azurin comprising amino acid sequence of SEQ ID NO: 6 and7.

Id. at pages 5-6. Claims 3, 4 and 8-11 are canceled in this response, without prejudice. Applicants respectfully traverse the rejection of claims 2, 5, 7 and 20.

Without acquiescing to the propriety of the Examiner's rejections and solely in an effort to further prosecution, claims 1, 2 and 5 have been amended to recite an azurin, a mutant azurin or a truncated azurin. Support for these amendments is found in the specification as filed. *See, e.g.,* paragraphs [014], [019-025] and [027-031] corresponding to Figures 4-10 and 12-15, respectively, [026], [071], [078], [081], [083-086] and [0112-0120]. Without acquiescing to the propriety of the Examiner's rejections and solely in an effort to further prosecution, claim 7 has been amended to recite, "wherein the mutant azurin

comprises the amino acid sequence selected from the group consisting of SEQ ID NOS: 6, 7, 45, 46, 47, 48, 50, 51, 52 and 53." Support for this amendment is found in the specification as filed. *See, e.g.,* paragraphs [083] and [0165].

A. The Examiner's rejection fails to separately address each claim.

The Examiner's analysis focuses entirely on the enablement requirement's application to claim 1. Notably absent from the Examiner's discussion of the rejection of claims 2, 5, 7 and 20 is any discussion of the limitations of claims 2, 5, 7 or 20. *See* Office Action of 8 August 2007 at pages 5-6. It is a matter of fundamental patent law that patentability is determined on a claim-by-claim basis; the Examiner ignores this most basic of principles and rejects eleven claims based upon an analysis of a single claim. For this reason alone, the Examiner's rejections of claims 2, 5, 7 and 20 should be reconsidered and withdrawn.

B. The Examiner errs by requiring in vivo data and deeming in vitro data insufficient

The Examiner states:

> [The] claimed invention is drawn to in vivo treating a condition with mutated or truncated azurin or any cupredoxin, however, the specification shows neither the result of in vivo treatment with the cupredoxin (except wild type azurin), nor correlation between the in vitro cytotoxic activities and in vivo treatment in a patient. Thus, in the absence of this guideline, direction and experimentations, one skilled in the art would be unable to use claimed invention without an undue quantity of experimentations because the unpredictability of the nature of the invention.

Office Action of 8 August 2007 at pages 6-7. The Examiner goes on to provide an analysis of the differences between in vivo and in vitro data. *Id.* at pages 8-10. The Examiner does not address the manner in which the law analyzes the two types of data. *See id.* As Applicants explained in their response to the Examiner's written description rejection, the law simply does not require in vivo testing data to support claims to the use of a compound to treat a patient. *See* MPEP § 2107.03. The Examiner's requirement is thus contrary to the law and improper. For this reason, Applicants respectfully request reconsideration and withdrawal of the Examiner's enablement rejections of claims 1, 2, 5, 7 and 20.

C. The Examiner errs in requiring that the subject compounds have identical properties

The Examiner states that "one skilled in the art has recognized that the mutated or truncated form of a toxin may not always have the same activities as its wild type form." Office Action of 8 August 2007 at page 7. The Examiner goes on to discuss the Yamada reference and a particular mutant that "has very little toxicity compared to the wild type of azurin" because it is "deficient in forming a complex with p53." *Id.* Based upon this, the Examiner concludes that "[b]ecause claimed invention for in vivo treatment a condition is unpredictable and because one skilled in the art has recognized the mutated azurins do not have the activities as wild type azurin undo experimentation would be necessary and required in order to use and practice claimed invention by one skilled in the art." *Id.*

Here, the Examiner is seemingly requiring the relevant genus of compounds to have identical functionalities or, perhaps more specifically, identical levels of functionality. However, the Examiner is incorrect in imposing such a requirement. Per the claims, the compounds must "promote death in a cell demonstrating resistance to cell death." Claim 1. That some compounds in the group do this better than others is not relevant to the enablement issue. Moreover, that some compounds in the genus are wholly inoperable is also not strictly relevant to the enablement inquiry. What is important is whether one of skill in the art could identify such embodiments without undue experimentation, which clearly is the case here. *See Atlas Powder Co. v. E.I. Du Pont*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *see also In re Dinh-Nguyen*, 492 F.2d 856, 858-59 (CCPA 1974) ("It is not a function of the claims to specifically exclude possible inoperative substances.").

D. The subject compounds share a common, highly conserved structure corresponding to their functionality

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971).

The cytotoxic cupredoxins are described in the specification as sharing a common, highly conserved structure which includes, *inter alia*, a beta-barrel structure, a copper binding site consisting of a cluster of four residues, and a hydrophobic patch involved in binding interactions with various partners, including p53. *See* paragraphs [073-085]. Additionally, as described above, it is known in the art that azurins have a G-H loop sequence which has great binding affinity for ephrinB2 and which exhibits a cytotoxic effect.

Thus, the specification disclosure contains a teaching of the manner and process of making and using the intention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented, as required under *In re Marzocchi*. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of claims 1, 2, 5, 7 and 20 under the enablement requirement of 35 U.S.C. § 112, first paragraph.

III. Claim rejections on the ground of nonstatutory obviousness-type double patenting

The Examiner has provisionally rejected claims 1, 3 and 20 as not patentably distinct from claims 19-22 of U.S. Patent Application Ser. No. 11/488,693, and has rejected claims 1-6 and 20 as not patentably distinct from claims 1-3, 5 and 7-12 of United States Patent Ser. No. 7,084,105 in view of Yamada *et al.* Office Action of 8 August 2007 at page 3. Claims 3, 4 and 6 are canceled in this response, without prejudice. Applicants respectfully traverse the rejection of claims 1, 2, 5, 7 and 20.

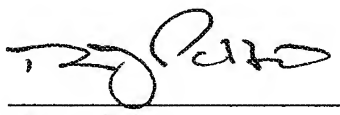
Applicants maintain their position that Examiner's rejections should be held in abeyance pending the allowance of claims. The Examiner has instructed that a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting ground. Without acquiescing to the propriety of the Examiner's rejections, and specifically the Examiner's interpretation of what the cited references teach or claim, Applicants respectfully and properly defer addressing the present rejection until there is allowable subject matter in the present application. At that time, a terminal disclaimer will be filed if warranted by the Examiner's rejection in view of the allowed claims.

CONCLUSION

Applicants have properly stated and traversed each of the Examiner's grounds for rejection. Applicants note that the Examiner has previously withdrawn all rejections over the prior art and that the claims are therefore free of the prior art. The Examiner's § 112 rejections have either been addressed by Applicants, or have been rendered moot by the claims canceled and amended in the present response such that the rejections no longer pertain to the presently claimed inventions. Accordingly, Applicants believe that the presented claims are in condition for allowance.

If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account.

Respectfully Submitted,



October 25, 2007

Don J. Pelto
Reg. No. 33,754

Sheppard Mullin Richter & Hampton LLP
1300 I Street NW
11th Floor East
Washington, DC 20005
Telephone: (202) 772-5362
Facsimile: (202) 312-9415